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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,818	01/06/2006	Koji Suematsu	283148US0PCT	3729

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
06/19/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,818	SUEMATSU ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 16-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,14,15 and 19-22* is/are rejected.

7)☒ Claim(s) *5-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/6/06; 9/18/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-8, 14, 15 and 19-22) in the reply filed on April 25, 2008 is acknowledged. The traversal is on the ground(s) that first, the restriction requirement did not show that the two inventions were patentably distinct or that there was burden associated with the search and examination of Groups I and II. Applicants further argue that the determining effect of the polymorphisms is not dependent on the particular polymorphism examined. This is not found persuasive because, first, the main criterion for the restriction requirement in the national phase case is a lack of unity, not distinct patentability or burden of search. However, both of these factors also apply here. First, the invention of Group II is drawn to any oligonucleotide from the sequence of an IRS2 gene, therefore an extremely large number of oligonucleotides, most of them unrelated to polymorphisms related to granulocytopenia. Therefore, the search for the oligonucleotides of Group II is not coextensive with the search for the methods of Group I. Further, as the polymorphisms are distinct, their association with granulocytopenia may vary, therefore examination of all of them is burdensome.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 9-13 and 16-18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 25, 2008.

3. Claims 1-8, 14, 15 and 19-22 will be examined.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on January 6, 2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

5. The information disclosure statement (IDS) submitted on September 18, 2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, references AZ and AAA will not be printed, as they are duplicates of references submitted in the January 6, 2006 IDS.

Claim Objections

6. Claims 5-8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4, 14, 15 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 1-3 are drawn to a method of linking the polymorphisms of the human insulin receptor substrate-2 (IRS2) gene to risk of granulocytopenia. However, the specification as

originally filed does not provide a description of where such polymorphisms are located. Specifically, Applicants state on page 13 and 14, paragraphs [0038]-[0039], that the IRS2 gene is included in the sequence with GenBank Accession No. AL162497, and the gene itself has accession No. XM_007095, and corresponds to bp 93,673-126,402 of the GenBank Accession No. AL162497. Applicants designated the positions of the polymorphic bases as follows (page 14, the end of the first paragraph):

"The position numbers of SNPs as described in the specification or the figure correspond to the position numbers counting from A of ATG that is used as a codon for Met at N-terminus of protein when mRNA is translated into protein (translation initiation codon)." Applicants did not indicate which bp of the XM_007095 is considered to be the A of the ATG codon.

Alignment of the sequences with GenBank Accession No. AL162497 and XM_007095 shows the following:

a) bp 1-3 of the cDNA for the IRS2 protein are "CGC", not "ATG".

b) Even if we assume that the numbering of SNPs starts with the first "C" (or G), there are still problems. For example, Fig. 1 indicates that the A29793G SNP is within exon 2. However, alignment of the cDNA for IRS2 and the AL162497 sequence indicates that exon 2 starts most likely at position 96,144 or 96,143. The bp 29,793 bp away from bp 126,402 would be bp 96,609, or about 450 bp away from exon 2. Further, bp 96,609 is an A on the strand shown, but a T on a complementary strand. Therefore, the positions of the primers to amplify this polymorphism, as listed in Table 8 on page 53, as spanning bp 96,070-96,091 (SEQ ID NO: 14) and bp 96,209-96,190 (SEQ ID NO: 13), do not make sense.

Therefore, Applicants did not provide an adequate written description of the invention.

9. Claims 1-4, 14, 15 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-4, 14, 15 and 19-22 are broadly drawn to methods of assessing the risk of drug-induced granulocytopenia by detecting a polymorphism of the human IRS2 receptor. However, as will be further discussed, there is no support in the specification and prior art for methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has a single working example in which subjects taking vesnarinone were examined for the presence of granulocytopenia associated with the drug and for polymorphisms in the IRS2 gene. Six polymorphisms, listed in Tables 1-6, were found to be significantly associated

with the onset of granulocytopenia. No other patients subject to other therapeutic regimens were examined for polymorphisms in the IRS2 gene and their possible association with granulocytopenia.

Guidance in the Specification.

The specification provides no evidence that the disclosed six polymorphisms in the IRS2 would be indicative of the risk for granulocytopenia in patients taking drugs or drug combinations other than vesnarinone. Further, as detailed below, it is not clear where in the sequence of the IRS2 gene are these polymorphisms located.

Applicants state on page 13 and 14, paragraphs [0038]-[0039], that the IRS2 gene is included in the sequence with GenBank Accession No. AL162497, and the gene itself has accession No. XM_007095, and corresponds to bp 93,673-126,402 of the GenBank Accession No. AL162497. Applicants designated the positions of the polymorphic bases as follows (page 14, the end of the first paragraph):

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Alignment of the sequences with GenBank Accession No. AL162497 and XM_007095 shows the following:

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The unpredictability of the art and the state of the art

No other references were found teaching or suggesting an association between granulocytopenia and IRS2 polymorphisms. However, three very recent references discuss a possible link between acquired granulocytopenia and polymorphisms in other genes. For example, Berliner et al. (Hematology, vol. 2004, pp. 63-79, 2004) discloses that in case of clozapine, tumor necrosis factor polymorphisms may play a role in the development of nutropenia (page 71, last two paragraphs; page 72, paragraphs 1-2 and Table 4).

Sugiyama et al. (J. Clin. Oncol., vol. 25, pp. 32-42, 2007) examined the link between neutropenia caused by the anticancer drug gemcitabine in combination with carboplatin, cisplatin or fluorouracil, and polymorphisms in the cytidine deaminase (CDA) gene. They concluded that haplotype *3 was correlated with an increased risk for neutropenia in patients undergoing multiple drug therapy (Abstract; Table 2; page 37, fourth paragraph; Table 7; page 38, fourth paragraph).

Finally, Hahn et al. (Am. J. Health. Syst. Pharm., vol. 63, pp. 2211-2217, 2006) teach that patients who are homozygous for the *28 allele of the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) experience severe toxicity, including neutropenia (Abstract; page 2213, paragraphs 5-10; page 2214, first paragraph; Table 1).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to allow the use of polymorphisms in the IRS2 gene in the diagnosis of the risk of granulocytopenia. First, all possible polymorphisms would have to be examined in the IRS2 gene, and then population studies with numbers of patients large enough to produce statistically significant results would have to be conducted for every drug and drug combination currently in use in clinical practice to treat any disease and correlated with the presence and/or absence of certain IRS2 polymorphisms. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the development of granulocytopenia in patients depends on a total genetic makeup of the patient as well as on the type of disease and drug being taken, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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Primary Examiner, Art Unit 1637
June 13, 2008